DEVELOPMENT AND VALIDATION OF STABILITY INDICATING ANALYTICAL METHODS FOR ESTIMATION OF PHARMACEUTICAL DRUGS BY QUALITY BY DESIGN APPROACH

A

SYNOPSIS

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1. ABSTRACT:

Quality-by-Design is a systematic approach to drug development, QbD tools and studies include prior knowledge, risk assessment, mechanistic models, design of experiments (DoE), data analysis and process analytical technology(PAT). FDA generalized quality by design in the field of pharmacy, which is based on the thorough understanding of how materials and process parameters affect the quality profile of final products. The application of QbD in drug formulation and process design is based on a good understanding of the sources of variability and the manufacture process.

The present study describes the development of comprehensive science and risk based HPLC method and subsequent validation for the analysis of active pharmaceutical ingredient(API) using a quality by design approach. The current state of analytical QbD in the industry is detailed with examples of application of analytical QbD. principles to arrange analytical methods including high performance liquid chromatography, quantitative color measurement and trace analysis for impurities.

Keywords: QbD, Analytical method, HPLC, Impurity analysis, chromatography, API

2. INTRODUCTION:

2.1 Stability testing of Drug substance

It requires an accurate analytical method that quantitates active pharmaceutical ingredients (API) without interference from degradation products process impurities and other potential impurities. With the advent of International Conference on Harmonization (ICH) guidelines, the requirement of establishment of stability-indicating assay method (SIAM) has become more clearly mandated. A stability-indicating assay is a validated quantitative analytical procedure that can detect the changes with time in the pertinent properties of the drug substance and drug product.[1]

2.2 Stability indicating Method Development using QbD

The concept of quality by design (QbD) in pharmaceutical industry has been introduced to enhance robust manufacturing process, to facilitate product quality, and to manufacture products in terms of "Six sigma. It is a system of practices developed for systematic improvement of processes, which eliminate the defects with statistical significance [4]. The stability-indicating method development using the Quality-by-Design (QbD) approach offers more accurate and robust results related to the OFAT (One Factor at a Time) approach, which comprises screening and optimization as steps[2].

The main aim of pharmaceutical industry is production of high quality product. QbD improves both the quality of final product and entire production process. One kye concept of AQbD is that the steps, tools, and approaches developed for application of QbD for manufacturing process.[3]

The quality can not be tested into product but can built in product. QbD is modern approach for quality of pharmaceuticals. Various quality and statistical tools and methods, such as statistical design of experiment, statistical quality control have been comprised in QbD. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle. This article explores the processes used in developing a market formulation and requisite supportive data, particularly in light of the industry's current movement toward submissions based on quality by design (QbD).[8]

Design of Experiments (DoE) are an important part of QbD, once it is considered to be an efficient tool to assess the conditions that enable a better performance of the formulations, using only a few experimental sets, requiring minimum investment and offering maximum return in terms of information. Process Analytical Technology (PAT) has an important role in QbD approach in order to control and guarantee the manufacturing process performance.[11]

Quality by Design (QbD) has become an important concept for the pharmaceutical industry that is further defined in the International Conference on Harmonisation(ICH) guidance on pharmaceutical development as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". Due to the poor pharmaceutical product quality, the first initiative was a step forward by the United States Food and Drug Administration (USFDA) for inculcation of quality paradigms into pharmaceutical development and regulatory practice[17].

Figure 1: Steps in QbD

2.3 QbD Principles[13]:

Drug development using the principles of QbD emphasizes a systematic approach and risk management approaches.

Two key concepts can be introduced for implementation and understanding of QbD.

The first concept is “design space.” ICH Q8 defines design.

It provide assurance of the quality of the data produced by the method.

Pharmaceutical QbD:

Quality by Design (QbD) is defined in the ICH Q8 guideline.

According to ICH Q8 guideline QbD as ‘a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Elements of QbD[9]:

QbD consists of the following parameters:

1. Quality Target Product Profile (QTPP)
2. Critical Quality Attributes (CQAs):
3. Critical Process Parameters (CPPs):
4. Critical Material Attributes (CMAs):

Opportunities of QbD[3]:

1. It validate the process
2. It reduces the cost
3. It increases the speed
4. It is easy, rapid and efficient

2.4 Steps for Pharmaceutical QbD implementation :

As a general rule, the practical implementation of QbD in the development of new pharmaceutical products can go through the following steps.

1. Define the desired performances of the product and identify the QTPPs;
2. Identification of the CQAs;

3. Identification of possible CMAs and CPPs;
4. Setup and execution of DoE to link CMAs and CPPs to CQAs and get enough information of how these parameters impacting QTPP.
5. Identify and control the sources of variability from the raw materials and the manufacturing process;
6. Continually monitor and to assure consistent product quality.

2.5 Tools of QbD[5]:

The commonly used tools in QbD, including

1. Risk assessment,
2. Design of experiment (DoE), and
3. Process analytical technology (PAT) .

2.6 Advantages Of QbD:

1. QbD is helpful for the conceptual understanding based on Product design goal, Process Design space, Control space and Operating space.
2. QbD, a regulatory and quality risk management.
3. Major safety and efficacy of various drug delivery systems can be ensured by the optimal use of QbD.
4. QbD tools facilitate a higher level of process understanding, root cause investigation and developing control strategies in the process and formulation development.
5. Science based understanding of the process results in minimized batch failure or rework along with better consistency and efficacy.

3.RATIONALE OF RESEARCH WORK

- By taking the idea from literature review we are decided to work on the analytical method development and validation by QbD approach.
- It provides us systematic guidance for different process like screening, optimization, degradation i.e. impurity studies.
- This process describes uses, safety, and efficacy of the product.
- The quality of product has been increasing by implementing tools such as Quality by Design and Process Analytical Technology.
- The effect of environmental factors on the stability of pharmaceutical product can be studied by increasing robustness of the method.

4. REVIEW OF LITERATURE:

CV Chandarana *et al.,* [3] (2022)

This article had reported the product quality has been a primary focus in the pharmaceutical industry. The quality by design (QbD) strategy contributes to higher productivity through the application of several approaches, such as process analytical technology (PAT), analytical target profiling (ATP), critical quality attribute (CQA) assessment, and quality target product profiling (QTPP) .

Livia Adalbert *et al.*,[4] (2022):

This article aims to provide an update on the current progress and emerging opportunities for additive manufacturing following the introduction of the new medical device regulation (MDR) within the EU. The advent of early-phase implementation of the Quality by Design (QbD) quality management framework in MD development is a focal point. The application of a regulatory supported QbD concept will ensure successful MD development, as well as pointing out the current challenges of 3D bioprinting.

Aayushi Rajora *et al.,* [5] (2021):

This article had a QbD approach studied the implications of various input variables (e.g. methodology parameters, and materials) of the merchandise development methodology, on the final word product (active pharmaceutical ingredient or drug product). The late QbD approach integrates the principles of QRM, and methodology analytical technology (PAT). QbD combined with methodology analytical technology (PAT) tools modify methodology management and increase assurance that the merchandise quality attributes unit of measurement achieved consistently. An integrated and risk-based approach for review of the merchandise development methodology is also a future need of the QbD plan. Although implementing the QbD approach is not a restrictive demand, restrictive agencies to supply flexibility in their pointers for producing that unit of measurement developed by the QbD approach.

Ashok K. Palakurthi *et al.,* [6] (2020)

This article had reported a simple reverse phase liquid chromatographic gradient method has been developed and validated for the simultaneous determination of specified & un-specified impurities of Telmisartan and Hydrochlorothiazide in combination oral solid dosage forms. The developed method is effective to separate a total of sixteen (16) peaks and quantify eleven (11)

specified impurities of Telmisartan and three (3) specified impurities of Hydrochlorothiazide with a minimum chromatographic resolution of 2.5. The separation was acquired with Inertsil ODS-3V, 150 × 4.6 mm, 3.5 µm column at a flow rate of 1.0 mL min^{-1} with the mobile phase-A consists of 0.02 M potassium dihydrogen phosphate (pH of 3.5) and mobile phase-B consists of a mixture of Milli-Q water and acetonitrile (100: 900 v/v) respectively.

Sarwar Beg et al.,[7] (2019):

In this context, the pharmaceutical industry has undergone a paradigm shift from traditional quality by testing (QbT) to the systematic quality by design (QbD) approach for attaining efficient development of drug products with enhanced quality and resource economics. The present article, in this regard, endeavors to provide an overview account on various facets of QbD in pharmaceutical development for ultimately attaining manufacturing excellence and regulatory compliance.

Buket Aksu *et al.*,[8](2019):

The Food and Drug Administration (FDA) is at the forefront of work in the field of "Quality by Design (QbD)," which implements regulatory intelligence to modernize the understanding and control of pharma manufacturing processes. The applications performed within the QbD approach, based on scientific data and with previous knowledge and experiences, are now part of the process for change with the flexibility of real-time release.

Lan Zhang *et al.*, [9](2017):

In this article, the basic knowledge of QbD, the elements of QbD, steps and tools for QbD implementation in pharmaceutics field, including risk assessment, design of experiment, and process analytical technology (PAT), are introduced briefly. Moreover, the concrete applications of QbD in various pharmaceutical related unit operations are summarized and presented.

Sherif I F Badawy *et al.*,[10] (2016) :

This article provides an integrated case study on the systematic application of QbD to product development and demonstrates the implementation of QbD concepts in the different aspects of product and process design for brivanib alaninate film-coated tablets. Using a risk-based approach, the strategy for development entailed identification of product critical quality attributes (CQAs), assessment of risks to the CQAs, and performing experiments to understand and mitigate identified risks. Quality risk assessments and design of experiments were performed

to understand the quality of the input raw materials required for a robust formulation and the impact of manufacturing process parameters on CQAs[24].

Daniela D'Almeida Peres *et al.,*[11] (2016)

This article had reported a multifunctional formulations are of great importance to ensure better skin protection from harm caused by ultraviolet radiation (UV). Despite the advantages of Quality by Design and Process Analytical Technology approaches to the development and optimization of new products, we found in the literature only a few studies concerning their applications in cosmetic product industry. Thus, in this research work, we applied the QbD and PAT approaches to the development of multifunctional sunscreens containing bemotrizinol, ethylhexyl triazone, and ferulic acid. In addition, UV transmittance method was applied to assess qualitative and quantitative critical quality attributes of sunscreens using chemometrics analyses.

Deepika Thakur *et al.,*[12](2016)

This article reported a anthocyanin has been proven to impart several health benefits and biological functions. Though, various analytical methods have been reported for single/multi-component analysis of anthocyanins, found to be tedious, time consuming and difficult to reproduce. Analytical studies on specific anthocyanins for estimation using an approach of Analytical Quality by Design are scarce. USP method is only reliable for cyanidin-3-O-glucoside (CY-3-O-Glu) estimation, but exploring many disadvantage of having high buffer concentration in mobile phase system and gradient elution, hence column blockage. So there is need to develop a novel HPLC method to overcome this problem with the use organic solvents with lesser volume of buffer in isocratic mode of elution. The aim is to develop a robust and precise method for estimation of CY-3-O-Glu in biopolymer based microcapsules and tablets. The optimized method consisted of mobile phase containing solvent A and B, flow rate 0.8 mL/min with 20 min of analysis time.

Serena Orlandini *et al.,*[32] (2013)

This article outlines the application of QbD concepts to the development of analytical separation methods, for example chromatography and capillary electrophoresis. QbD tools, for example risk assessment and design of experiments, enable enhanced quality to be integrated into the analytical method, enabling earlier understanding and identification of variables affecting method performance. A QbD guide is described, from identification of quality target product

profile to definition of control strategy, emphasizing the main differences from the traditional quality by testing (QbT) approach.

M. Vamsi Krishna *et al.*,[16](2012)

This article had reported Stability of eberconazole nitrate (EBZ) was investigated using a stability indicating HPLC method. Quality by Design (QbD) approach was used to facilitate method development. EBZ was exposed to different stress conditions, including hydrolytic (acid, base, neutral), oxidative, thermal and photolytic. Relevant degradation was found to take place in all the conditions. The degradation of EBZ followed (pseudo) first-order kinetics under experimental conditions. The kinetic parameters (rate constant, $t_{1/2}$, and t_{90}) of the degradation of EBZ were calculated.

Frederick G. Vogt *et al.*,[13] (2010):

In this article, the current state of analytical QbD in the industry is detailed with examples of the application of analytical QbD principles to a range of analytical methods, including high-performance liquid chromatography, Karl Fischer titration for moisture content, vibrational spectroscopy for chemical identification, quantitative colour measurement, and trace analysis for genotoxic impurities.

5. IMPORTANCE OF THE STUDY:

- This study facilitates an understanding of risk management method.
- The QbD methodology promotes a better understanding of material characteristics and process parameters that affect the final quality of the targeted product.
- The present study will also indicate the importance of QbD approach and its implementation in the preparation and optimization of Pharmaceutical dosage form.
- The importance of study is to improve patient compliance and enhance effectiveness of treatment by formulating pharmaceutical dosage form.

6. AIM AND OBJECTIVE :

AIM:

Development And Validation Of Stability Indicating Analytical Method For Estimation Of Pharmaceutical Drug By Quality By Design Approach.

OBJECTIVES:

- To formulate, evaluate and optimize the active pharmaceutical ingredient by Quality by Design.
- To develop and validate active Pharmaceutical Ingredient by HPLC.
- To apply QbD approach using statistical design of experiment(DoE) to develop method.
- To validate the developed analytical method according to ICH Q2 guidelines for the below mentioned parameters
    - Accuracy
    - Linearity
    - Precision
    - LOD (Limit of Detection)
    - LOQ (Limit of Quantification)
    - Specificity
    - Robustness
- Increases efficiency, lower cost, avoid risk.
- To carry out forced degradation study on API.

7. METHODOLOGY:

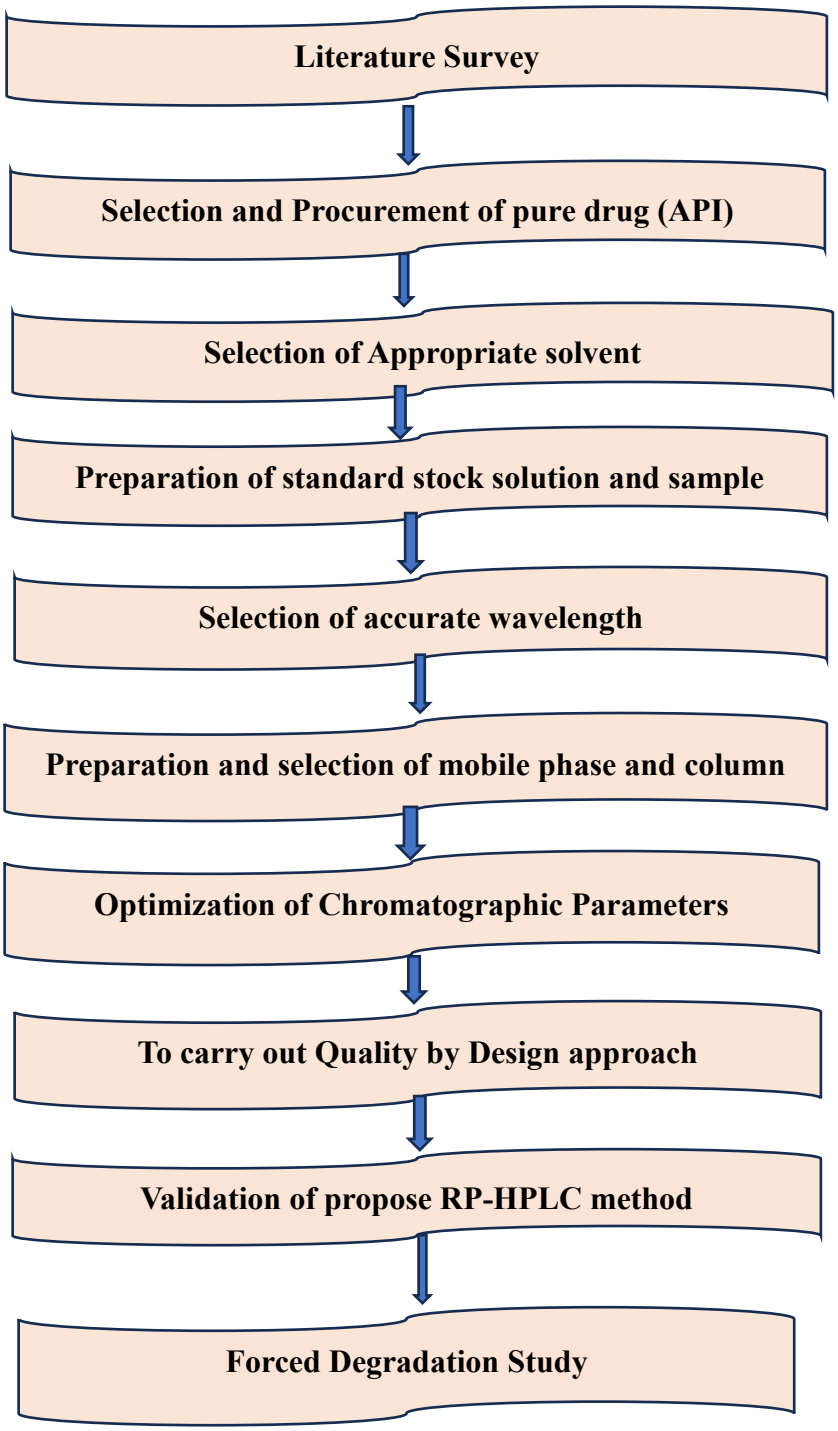
Literature Survey
Selection and Procurement of pure drug (API)
Selection of Appropriate solvent
Preparation of standard stock solution and sample
Selection of accurate wavelength
Preparation and selection of mobile phase and column
Optimization of Chromatographic Parameters
To carry out Quality by Design approach
Validation of propose RP-HPLC method
Forced Degradation Study

Figure2 : Flow chart of Research methodology

7.RESEARCH WORK PLAN

Sr. No.	Work	Period
1	Literature Survey	6 Months
2	Procurement of API and Excipient	2 Months
3	Selection of Solvent to be used	2 Months
4	Preparation of Standard Stock Solution and Sample Solution	1 Months
5	Selection of wavelength and Preparation & Selection of Mobile Phase	1 Months
6	Optimization of Chromatographic Conditions	3 Months
7	Implementation of Quality by Design Approach	6 Months
8	Validation of Propose RP-HPLC Method	6 Months
9	Forced Degradation Study	3 Months
10	Other Suggested Work and Compilation of Data	6 Months
	Total Duration of Work	36Months

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